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The 5-HT$_{1A}$ Receptor and the Stimulus Effects of LSD in the Rat

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Abstract

Rationale—It has been suggested that the 5-HT$_{1A}$ receptor plays a significant modulatory role in the stimulus effects of the indoleamine hallucinogen lysergic acid diethylamide (LSD).

Objectives—The present study sought to characterize the effects of several compounds with known affinity for the 5-HT$_{1A}$ receptor on the discriminative stimulus effects of LSD.

Methods—12 Male F-344 rats were trained in a two-lever, fixed ratio10, food reinforced task with LSD (0.1 mg/kg; IP; 15 min pretreatment) as a discriminative stimulus. **Combination and substitution tests** with the 5-HT$_{1A}$ agonists, 8-OH-DPAT, buspirone, gepirone, and ipsapirone, with LSD-induced stimulus control were **then performed**. The effects of these 5-HT$_{1A}$ ligands were **also** tested in the presence of the selective 5-HT$_{1A}$ receptor antagonist, WAY-100,635 (0.3 mg/kg; SC; 30 min. pretreatment).

Results—In combination tests stimulus control by LSD was increased by all 5-HT$_{1A}$ receptor ligands with agonist properties. Similarly, in tests of antagonism**,** the increase in drug-appropriate responding caused by stimulation of the 5-HT$_{1A}$ receptor was abolished by administration of WAY-100,635.

Conclusions—These data, obtained using a **drug discrimination** model of the hallucinogenic effects of LSD, provide support for the hypothesis that the 5-HT$_{1A}$ receptor has a significant modulatory role in the stimulus effects of LSD.

Keywords

Lysergic acid diethylamide [LSD]; Drug discrimination; rat; 8-OH-DPAT; buspirone; gepirone; ipsapirone; WAY-100, 635

Introduction

Currently there are fourteen recognized 5-HT receptor subtypes which fall into 7 families, 5-HT$_{1–7}$ (Raymond 2001). Although serotonergic systems are clearly relevant to the effects of LSD, questions still remain as to the contributions of specific serotonergic receptor subtypes (Winter et al. 1999). The blockade of the stimulus effects of LSD by administration of 5-HT$_2$ receptor antagonists as well as a correlation between affinity of the 5-HT$_2$ receptor and hallucinogenic potency in man led Glennon and colleagues (1984) to hypothesize that hallucinogens act as 5-HT$_2$ agonists. In support of this idea Schreiber and colleagues (1994) found that the 5-HT$_{2A}$ receptor antagonist, MDL 100,907, but not the 5-HT$_{2C}$ receptor antagonist, SB 200,646, blocked the stimulus effects of the phenylalkylamine hallucinogen 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI). However, affinity at the 5-HT$_{2A}$ receptor could only account for 56% of the variability in the potency of an antagonist to block

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the stimulus effects of LSD *in vivo* (Fiorella et al. 1995a). Furthermore, compounds such as quipazine have high affinity for the 5-HT_{2A} receptor yet are not hallucinogenic (Fiorella et al. 1995b; Egan et al. 1998). Thus, while 5-HT_{2A} receptor stimulation is a necessary component of LSD-induced stimulus control, it is not the only mechanism by which the drug exerts its effects.

It has been suggested that functional interactions exist among the different populations of 5-HT receptors and that stimulation of one receptor subtype may influence the activity of another. 5-HT_{2A} mediated behaviors have been shown to be influenced by the 5-HT_{1A} receptor in a variety of experimental paradigms. For example, the head-twitch response, a behavior typically associated with 5-HT_{2A} receptor stimulation (Green et al. 1983; Schreiber et al. 1995b), has been shown to be variably affected by 5-HT_{1A} agonism. Prior research has found that quipazine induced head twitches are increased by the administration of the 5-HT_{1A} agonist, gepirone (Eison et al. 1986; Yocca et al. 1991). However the effects of 5-HT_{1A} agonism on this behavioral outcome are unclear as other investigations have shown that 8-hydroxy-2-(di-*N*-propylamino)tetralin (8-OH-DPAT) is able to significantly decrease DOI mediated head twitches (Darmani et al. 1989). 8-OH-DPAT is the prototypical 5-HT_{1A} receptor agonist and has an affinity for the 5-HT_{1A} receptor which is several hundred-fold greater than for the 5-HT_2 receptor (Hamon 1984, 1986; Winter and Rabin 1987; Gozlan et al. 1988). Further complicating matters is a report showing that 8-OH-DPAT is able to increase 5-MeO DMT-induced, but not 5-hydroxytryptophan-induced, head-twitch response in rats (Darmani et al. 1989). In addition isobolographic analysis suggests that 5-HT_{1A} and 5-HT_{2A} receptors act antagonistically with regards to their locomotor suppressing effects (Krebs-Thompson and Geyer 1998). While complex, the relationship between 5-HT_2 and 5-HT_{1A} receptors seems to be of a reciprocal nature. This is evident from studies showing that 8-OH-DPAT-induced forepaw treading is increased 20 fold by administration of DOI (Arnt and Hyttel 1989).

The 5-HT_{1A} receptor has been implicated in a variety of CNS responses and may play a role in depression and the formation of memory (Winter and Petti 1987; Sarnyai et al. 2000; Gingrich and Hen 2001; Hoyer at al. 2002). **It has also been suggested that 5-HT1A receptors mediate the behavioral effects of the anxiolytics buspirone and ipsapirone (Cunningham et al. 1987a).** The present study sought to characterize the effects of the 5-HT_{1A} ligands 8-OH-DPAT, buspirone, gepirone, (Eison et al. 1986) and ipsapirone (Traber and Glaser 1987) on the discriminative stimulus effects of LSD.

Materials and Methods

Subjects

12 Male Fischer 344 rats were obtained at an age of approximately 6 weeks from Harlan Sprague-Dawley Inc. (Indianapolis, Ind., USA), housed in pairs under a 12-h light-dark cycle beginning at 6:00 a.m., and allowed free access to water in their home cages. All training and testing took place during the light cycle. Subjects were fed standard rat chow following experimental sessions. Caloric intake was controlled to maintain a mean body weight of 250 g. Caloric control has been shown to lengthen the life span and decrease the incidence of a variety of pathologies in Fischer 344 rats (Keenan et al.1994). Animals used in these studies were maintained in accordance with US Public Health Service Policy on Humane Care and Use of Laboratory Animals as amended August 2002. All experimental protocols were approved by the Institutional Animal Care and Use Committee of the **State University of New York at Buffalo.**

Apparatus

Six small animal test chambers (Med Associates ENV-008) were used for all experiments. These were housed in larger light-proof, sound-insulated boxes which contained a house light and an exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper that delivered 0.1 ml of sweetened condensed milk diluted 2:1 with tap water. Sessions were managed by a micro-computer using operant control software (MED-PC State Notation, Version IV).

Training procedures

After learning to drink from the dipper, rats were trained to press first one and then the other of the two levers. The number of responses for each reinforcement was gradually increased from 1 to 10. During this time, the reinforced lever was alternated on a random basis. All subsequent training and testing sessions used a fixed-ratio 10 (FR10) schedule of reinforcement **and a 10 minute training session**. Discrimination training was then begun. Subjects were trained to discriminate LSD [0.1 mg/kg, 15 min pretreatment time, intraperitoneal (IP) injection] (Hirschorn and Winter 1971; Fiorella et al. 1995b) from saline. Following the administration of drug, every tenth response on the drug-appropriate lever was reinforced. Similarly, responses on the saline-appropriate lever were reinforced on a FR10 schedule following the injection of saline. For half of the subjects, the left lever was designated as the drug-appropriate lever. During discrimination training, drug and saline were alternated on a daily basis. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses prior to the delivery of the first reinforcer were on the appropriate lever, i.e. no more than two incorrect responses prior to completion of the FR10 on the correct lever. **After stimulus control was established tests were conducted once per week in each animal so long as performance did not fall below the criterion level of 83% correct responding in any one of the three previous training sessions**.

Combination and substitution tests

After stimulus control with LSD was well established, **combination and substitution** tests were conducted once per week in each animal **if the criterion for drug-induced stimulus control were met**. Tests were balanced between subjects trained on the previous day with saline and drug, respectively. During test sessions, no responses were reinforced and the session was terminated after the emission of ten responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Response rate was calculated by dividing the total number of responses emitted prior to lever selection, that is, prior to the emission of ten responses on either lever, **divided by elapsed time.** Data for any subjects failing to emit ten responses within the constraints of the 10-min test session were not considered in the calculation of the percent drug-appropriate responding but were included in the analysis of response rates.

The effects of 5-HT_{1A} agonists on LSD-induced stimulus control were assessed by co-administration of a 5-HT_{1A} agonist [15 min. pretreatment, subcutaneous injection (SC)] and LSD (15 min before testing) as previously described (Winter et al. 2000). The interactions of 5-HT_{1A} ligands and WAY-100,635 with stimulus control by LSD were assessed in experiments in which WAY-100,635 was administered 30 min, SC, before testing and the **combination of LSD and a** 5-HT_{1A} agonist were administered 15 min before testing. For purposes of discussion an intermediate degree of antagonism is defined as less than 80% drug-appropriate responding and significantly different from both training conditions.

Drugs

Lysergic acid diethylamide [(+)-LSD (+)-tartrate (2:1)] was generously provided by the National Institute on Drug Abuse, Rockville, Md., USA. 8-hydroxy-2-(di-*N*-propylamino) tetralin, WAY-100,635, and buspirone were purchased from Tocris, USA. Gepirone and ipsapirone were gifts from Bristol-Meyers Squibb Company, Wallingford, CT and Miles Pharmaceuticals, West Haven, CT, respectively. Doses are expressed as mg/kg **and refer to weights of the salts**. LSD and the 5-HT_{1A} ligands were dissolved in bacteriostatic water.

Statistical analysis

The statistical significance of **combination tests with** a 5-HT_{1A} agonist and LSD were determined using two-way ANOVA with dose of LSD and treatment with the 5-HT_{1A} agonist as factors. **Two-way ANOVA was also used to determine the statistical significance of the antagonism of the effects of the 5-HT1A agonists on LSD induced stimulus control by WAY-100,635. In combination tests involving WAY-100,635, dose of LSD and treatment with the combination of 5-HT1A ligands were used as factors.** For assessment of the statistical significance of antagonism of the stimulus effects of **the training dose of** LSD, by WAY-100,635 one-way ANOVA was used to compare the two training conditions **(saline and 0.1 mg/kg LSD)** with the combination of LSD and WAY-100,635. **In all measures of analysis of variance** subsequent multiple comparisons were made by the method of Student-Newman-Keuls. **For analysis of individual points in substitution tests Student's t-test was used.** Differences were considered to be statistically significant if the probability of their having arisen by chance was <0.05. All analyses were conducted using SigmaStat 2.03 for Windows (Jandel Scientific Software, San Rafael, Calif., USA). Data **for LSD and saline training sessions** were repeated for each comparison and statistical analyses were applied using the appropriate **training** sessions. However, for purposes of clarity, mean values for **training sessions** are shown in all figures.

Results

Initial experiments determined the effects of 8-OH-DPAT when administered to LSD-trained animals. A maximum of 53.2% LSD-appropriate responding was achieved with the highest dose of 8-OH-DPAT tested (1.0 mg/kg) although significant impairment of test subjects resulted in only 9 of 12 animals completing the test session. Rate suppression precluded us from testing higher doses. One-way ANOVA revealed that the highest dose of 8-OH-DPAT yielded a level of drug-appropriate responding which was significantly different from both the training dose of LSD and saline (i.e., intermediate substitution) [$F(2,30)=52.331$; $p=0.001$]. The effects of **the highest dose of** 8-OH-DPAT on rate of responding and LSD substitution were blocked by the selective 5-HT_{1A} receptor antagonist WAY-100,635 [Student's t-test, p=.044 and p=.002, respectively] (Forster et al. 1995; Fletcher et al. 1996). However, when combined with the training dose of LSD, **one-way ANOVA revealed that** WAY-100,635 had no effect on drug-appropriate responding **although there was a significant rate suppressant effect [$F(2,34)=9.978$; $p<0.001$].** A dose of 0.05 mg/kg 8-OH-DPAT was chosen for subsequent experiments as this dose yielded a degree of LSD-appropriate responding which did not differ significantly from that following the injection of saline. The rate of responding was not significantly decreased at this dose, and all subjects were able to complete the test session.

Figure 2 shows a dose-related increase in LSD-appropriate responding in rats trained and tested with LSD. When the same doses were tested in rats pretreated with a fixed dose of 8-OH-DPAT (0.05 mg/kg), LSD-appropriate responding increased for all doses of LSD less then the training dose (0.01 mg/kg and 0.03 mg/kg). Two-way ANOVA showed a significant increase in LSD-appropriate responding following the combination of LSD and 8-OH-DPAT compared with

LSD alone [F(1,47)=9.057; p=0.004]. **Neither the effect of dose nor the interaction term were significant.** A significant decrease in the rate of responding was also seen with the combination of LSD and 8-OH-DPAT [F(1,47)=13.67; p<0.001] **although the effects of dose and the interaction term did not reach significance**. Although displaying a much higher affinity for the 5-HT_{1A} receptor versus other subtypes, 8-OH-DPAT has been shown to be a partial agonist at the 5-HT_7 receptor and have affinity for the α_2-adrenoceptor (Winter and Rabin 1992;Ruat et al. 1993;Wood et al. 2000). To rule out the possibility of effects caused by administration of 8-OH-DPAT other then 5-HT_{1A} receptor stimulation, WAY-100,635 (0.3 mg/kg) was used. Upon administration of the combination of 8-OH-DPAT, LSD, and WAY-100,635 drug-appropriate responding returned to levels which were not significantly different from LSD administered alone **as measured by two-way ANOVA. However, a suppression of rate of responding was still seen with the combination of 8-OH-DPAT, LSD, and WAY-100,635 [F(1,47)=16.25; p<0.001]. In a manner similar to drug-appropriate responding, neither the effect of dose, nor the interaction term were significant.**

A similar potentiation of LSD-appropriate responding caused by administration of the clinically effective anxiolytic buspirone (Riblet et al. 1982; Goa and Ward 1986) is seen in figure 3. Buspirone has been shown to possess agonist activity and be relatively specific for receptors of the 5-HT_{1A} receptor subtype (Riblet et al. 1982; Dourish et al. 1986). A dose of buspirone of 0.3 mg/kg was chosen for **combination tests** as this dose resulted in a level of LSD-appropriate responding which was not significantly different from that achieved with the injection of saline. When a dose-response curve was performed with doses of LSD less then the training dose (0.01 mg/kg and 0.03 mg/kg), the addition of buspirone (0.3 mg/kg) resulted in an increase in drug-appropriate responding. Two-way ANOVA revealed that the increase in LSD-appropriate responding was significant in comparison to LSD given alone [F(1,43) =23.46; p<0.001] **while the effects of dose of LSD were significant [F(1,43)=5.865; p=.020] the interaction term was not.** A significant decrease in rate of responding was also seen with the combination of LSD and buspirone [F(1,47)=16.28; p<.001] **although neither the effect of dose, nor the interaction term were significant**. However, when WAY-100,635 (0.3 mg/kg) was added to the combination of LSD and buspirone **two-way ANOVA determined that** drug-appropriate responding and rate of responding returned to levels which were not significantly different from LSD administered alone.

Figure 4 shows an orderly dose-related increase in LSD-appropriate responding in rats trained and tested with LSD. **Substitution tests** revealed that a 0.3 mg/kg dose of gepirone resulted in a level of LSD-appropriate responding which did not differ from that following the administration of saline. As was true for buspirone and 8-OH-DPAT, when doses of LSD less then the training dose of LSD were administered in the presence of a fixed dose of gepirone (0.3 mg/kg) an increase in drug-appropriate responding occurred. This increase was statistically significant as measured by two-way ANOVA [F(1,45)=4.227; p=0.046] **the effects of dose were significant [F(1,45)=7.6; p=0.008] although the interaction term was not**. A significant decrease in the rate of responding was also observed [F(1,47)=31.80; p<0.001] **with a non-significant effect of dose, and interaction term**. The effects of gepirone on LSD-appropriate responding were reversed by administration of WAY-100,635 (0.3 mg/kg), **however gepirone's effects on rate suppression remained unchanged and were significantly reduced in comparison to LSD given alone [F(1,47)=28.72; p<0.001].**

Based upon its high affinity for the 5-HT_{1A} receptor (Dompert et al. 1985), ipsapirone was also screened for potential interactions with the LSD stimulus cue. A dose of 0.3 mg/kg was chosen **for combination tests** as this dose resulted in a level of drug-appropriate responding which did not differ from that following the injection of saline. Results of the combination of ipsapirone (0.3 mg/kg), with a range of LSD doses are shown in figure 5. For LSD doses of

0.01 and 0.03 mg/kg, two-way ANOVA revealed a significant increase in LSD-appropriate responding following the combination of LSD and ipsapirone compared with LSD alone [$F(1,38)=4.488$; $p=0.041$] **with a significant effect of dose [$F(1,38)=4.25$; $p=0.047$] and non-significant interaction term** . An additional, significant, rate suppressing effect was also seen by administration of **the combination of** ipsapirone and LSD [$F(1,43)=24.05$; $p<0.001$] **although neither dose, nor the interaction term were significant. Two-way ANOVA determined that** the effects of ipsapirone on the LSD appropriate responding and rate suppression were eliminated by pretreatment with the 5-HT_{1A} antagonist WAY-100,635 (0.3 mg/kg).

Discussion

The data of figure 1 are a confirmation of our previous findings showing the partial substitution of LSD to the 8-OH-DPAT stimulus cue (Winter and Rabin 1987). While Cunningham and Appel (1987b) failed to produce substitution between these two compounds, procedural differences may account for this discrepancy as the latter study utilized a different strain of rat, lower dose of the training agent (0.08 mg/kg LSD) and higher FR schedule (FR 20). The intermediate level of LSD substitution achieved with 8-OH-DPAT in the present investigation indicates that 8-OH-DPAT and LSD share a common stimulus component. However, 5-HT_{1A} receptor stimulation seems to be a non-essential component of the LSD stimulus cue because the training dose of LSD was unaffected by WAY-100,635. Thus it would seem that LSD produces effects on 5-HT_{1A} receptors which become apparent in drug discrimination studies when drugs which are active at 5-HT_{1A} receptors are tested. Although the salient characteristics of LSD induced stimulus control are mediated via agonist actions at 5-HT_{2A} receptors (Fiorella et al. 1995a), the data shown in Fig. 1 suggest that an additional, albeit smaller role is played by the 5-HT_{1A} receptor.

The 5-HT_{1A} receptor is found throughout the brain, with high concentrations in dorsal raphe nucleus (DRN), medial raphe nucleus (MRN), hippocampus, lateral septum, entorhinal cortex, and central amygadala. The raphe nuclei are the major source of serotonergic cell bodies in the brain and send projections to cortical and limbic areas (Aghajanian et al. 1968). In general, projections from DRN and MRN overlap one another with the former sending projections to the frontal cortex (Molliver 1987) an area containing a high density of 5-HT_{2A} receptors (Pazos and Palacios 1985) and thought to play a significant role in hallucinogenesis and psychosis (Arvanov et al. 1999; Gewirtz and Marek 2000). Studies in our laboratory support a role of the medial raphe nucleus in hallucinogenesis as systemically administered (-) **2,5-dimethoxy-4-methylamphetmine (DOM)** generalized completely to DOM infused into this area (Doat et al. 2003). Indeed, LSD is known to produce a complete inhibition of neuronal activation within the raphe nucleus (Aghajanian and Haigler 1975) which would likely affect the activity of downstream cortical neurons and contribute to the drug's effects. Although suppression of neurons within the raphe nucleus does not seem to be a tenable hypothesis for the primary mechanism of hallucinogenesis, it may be important for the overall psychopharmacology of psychotropic compounds (Nichols 2004). A similar conclusion was reached by Penington and Fox (1994) who suggested that inhibition of 5-HT release resulting from 5-HT_{1A} receptor activation may play a role in the hallucinogenic actions of LSD.

A previous investigation has found a potentiation of the phenethylamine hallucinogen DOM by pretreatment with 8-OH-DPAT (Glennon 1991). Prior research examining the head twitch response and its interaction with 5-HT_{1A} agonists has found that quipazine induced head twitches were increased by the administration of gepirone (Darmani et al. 1989; Yocca et al. 1991). DOI induced ear scratch stereotypy (another behavior thought to be mediated via 5-HT_{2A} receptor stimulation) was also increased by administration of 8-OH-DPAT (Darmani et al. 1990). These data suggest a potentiation of 5-HT_{2A} function caused by 5-HT_{1A} agonism

and is fully in keeping with the results in fig. 2–5. The precise mechanism by which this potentiation occurs however remains obscure.

Several other investigations have been made into the complex mechanism of action of LSD. Considering its relatively non-selective binding profile it is not surprising that numerous pharmacological stimuli are able to affect the stimulus properties of LSD. Studies in our laboratory have demonstrated that the stimulus effects of LSD are modulated by 5-HT_{2C} receptors, (Fiorella et al. 1995a) significantly reduced by the antipsychotic clozapine (Palumbo and Winter 1994), and potentiated by selective serotonin reuptake inhibitors (SSRI's) (Fiorella et al. 1996). The last observation is interesting in light of data suggesting that the efficacy of antidepressant therapies and the azapirone anxiolytics may be due to region specific changes in 5-HT_{1A} receptor function (Hensler 2002) and that the decrease in the subjective effects of LSD following chronic treatment with serotonergic antidepressants may involve changes in 5-HT_{1A} receptor sensitivity (Bonson et al. 1996). These findings suggest that manipulation of serotonergic neurotransmission can affect the behavioral outcome of LSD administration. To our knowledge, this is the first report to show the potentiation of the stimulus properties of LSD with multiple compounds having agonist actions at the 5-HT_{1A} receptor.

Schreiber and colleagues (1995) have correlated the ability of a drug to substitute for the 8-OH-DPAT stimulus cue with its affinity for the 5-HT_{1A} receptor. 8-OH-DPAT has previously been shown to generalize to ipsapirone, buspirone, and gepirone (Winter 1988; Winter and Rabin 1989; Rabin and Winter 1993) all of which have appreciable selectivity for the 5-HT_{1A} receptor with pK_D values ranging from 8.90-7.49 (Eison et al. 1986; Traber and Glaser 1987; Rabin and Winter 1993). These data suggest that the primary stimulus component of these compounds is mediated via 5-HT_{1A} stimulation and that all have similar stimulus properties. The fact that the observed potentiation of the LSD stimulus cue by 5-HT_{1A} agonists was completely reversed by WAY-100,635 further supports this hypothesis.

In vitro studies have also demonstrated similarities among the 5-HT_{1A} ligands tested. Electrophysiological experiments have shown that application of 8-OH-DPAT, buspirone, or gepirone all result in the suppression of firing of neurons within the DRN through activation of $G_{i/o}$ proteins (Innis and Aghajanian 1987; Blier et al. 1993). Suppression of raphe firing and second messenger systems may be a potential mechanism by which the ligands studied are able to potentiate the stimulus effects of LSD. Microdialysis studies have shown that buspirone and ipsapirone mimic one another in their ability to enhance dopamine outflow within the prefrontal cortex of the rat (Wedzony et al. 1996). **Although it appears buspirone produced the largest amount of potentiation of the LSD stimulus cue,** the sum of these data indicate that the agonists used in this study have similar pharmacological properties. Subtle differences in the mechanisms of action of these compounds may account for the slight differences in the levels of potentiation observed with each compound.

In summary, it has been demonstrated that 5-HT_{1A} receptor agonists are able to increase the stimulus effects of LSD. This supports the idea that the 5-HT_{1A} receptor plays a modulatory role in the stimulus effects of LSD. The exact mechanism of this increase is unknown, although it likely involves modulation of serotonergic neurotransmission and 5-HT_{2A} receptor function. Further study of this receptor subtype may offer a greater understanding of its functional role with respect to hallucinogens and the etiology of numerous psychiatric disorders. A suggestive role for the 5-HT_{1A} receptor for increasing the efficacy of current antipsychotic medications has been proposed (Meltzer 1999). Indeed, it has been suggested that the atypical profile of the antipsychotic aripiprazole may be derived in part, from its 5-HT_{1A} agonist effect (Marona-Lewicka and Nichols 2004). Further investigation is needed to determine the precise role of this receptor in the mechanism of action of LSD and other psychotomimetic substances.

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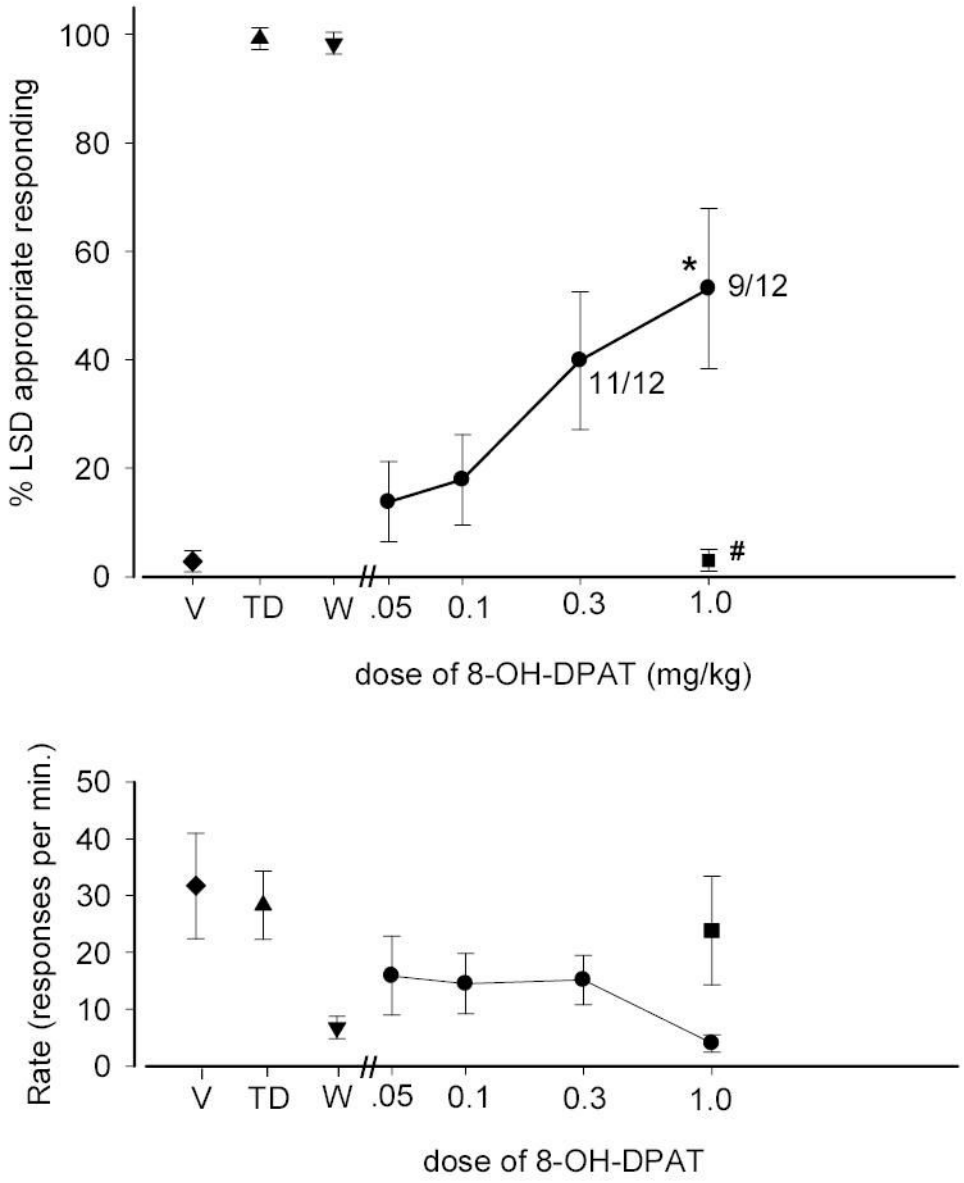

Fig. 1.

Effects of 8-OH-DPAT, the selective 5-HT_{1A} antagonist WAY-100,635, and their combination in rats trained to discriminate LSD (0.1 mg/kg) from saline. **The *diamond* represents the effects of water administered IP 15 min before testing.** *Circles* represent the effects of 8-OH-DPAT administered IP 15 min. before testing. The *Square* represents the effects of 8-OH-DPAT in the presence of WAY-100,635 (0.3 mg/kg, SC, 30 min pretreatment). The *Triangle* represents the training dose of LSD. The *Inverted Triangle* represents the effects of the training dose of LSD given in the presence of WAY-100,635. Each point represents the mean of one determination in each of 12 rats. Standard errors of the mean are shown. * Significantly different from both training conditions. # Significantly different from 8-OH-DPAT (1.0 mg/kg). *Ordinate: upper panel:* percent LSD-appropriate responding; *lower panel:* rate expressed as responses per minute. *Abscissa:* dose plotted on a log scale.

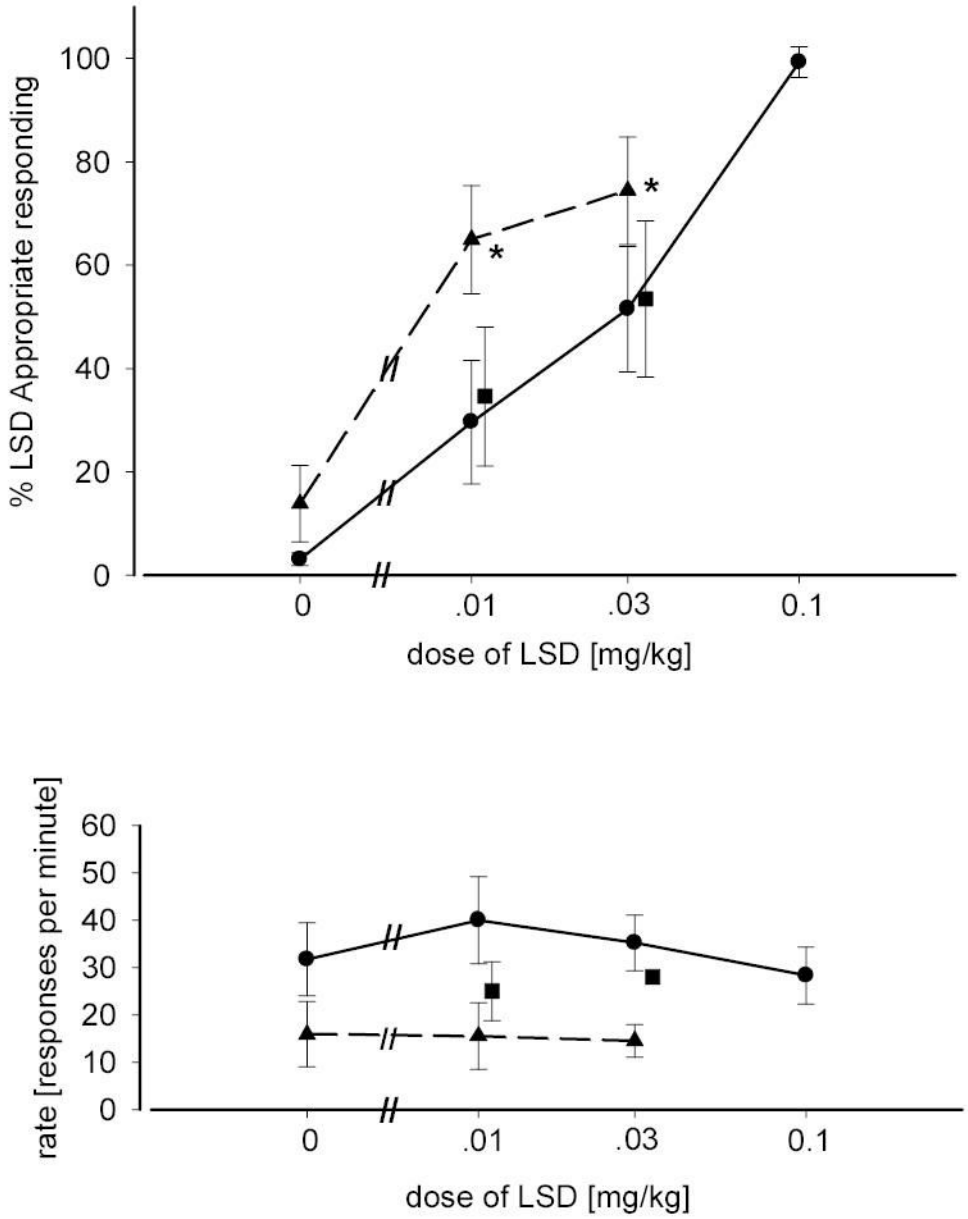

Fig. 2.

Dose-response relationship for LSD alone and in combination with 8-OH-DPAT. *Circles* represent the effects of LSD alone in rats trained with LSD as a discriminative stimulus (0.1 mg/kg). *Triangles* represent the effects of LSD in combination with 8-OH-DPAT (0.05 mg/kg). *Squares* represent the effects of LSD following treatment with 8-OH-DPAT and WAY-100,635 (0.3 mg/kg). LSD was administered IP 15 min. before testing. 8-OH-DPAT and WAY-100,635 were administered SC 15 min and 30 min respectively, before testing. Each point represents the mean of one determination in 12 rats. Standard errors of the means are indicated. * Significantly different from LSD given alone. *Ordinate: upper panel:* percent LSD-appropriate responding; *lower panel:* rate expressed as responses per minute. *Abscissa:* dose plotted on a log scale.

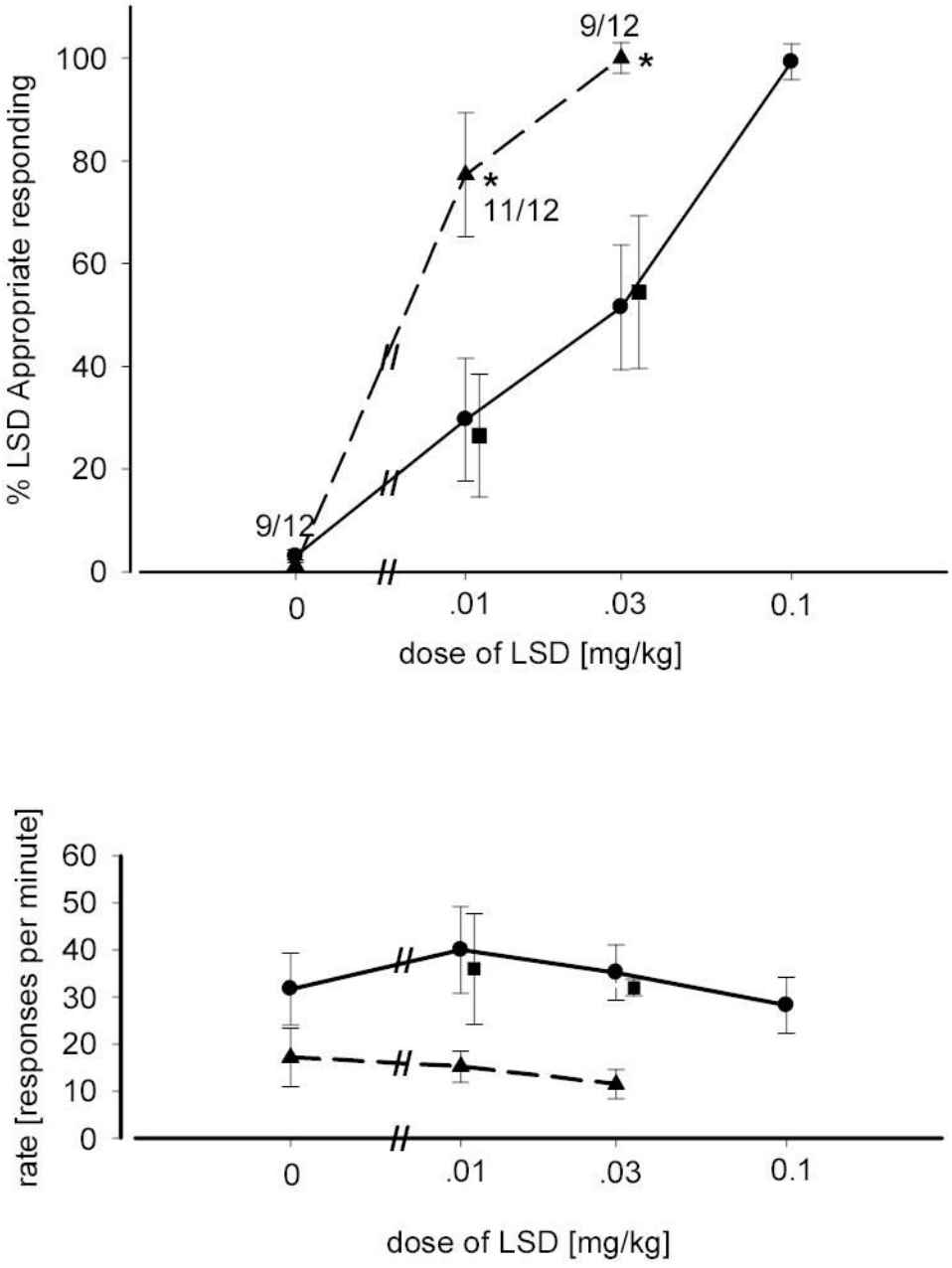

Fig. 3.

Dose-response relationship for LSD alone and in combination with buspirone. *Circles* represent the effects of LSD alone in rats trained with LSD as a discriminative stimulus (0.1 mg/kg). *Triangles* represent the effects of LSD in combination with buspirone (0.3 mg/kg). *Squares* represent the effects of LSD in combination with buspirone and WAY- 100,635. Number of subjects completing each session are indicated. Other details are as described in figure 2.

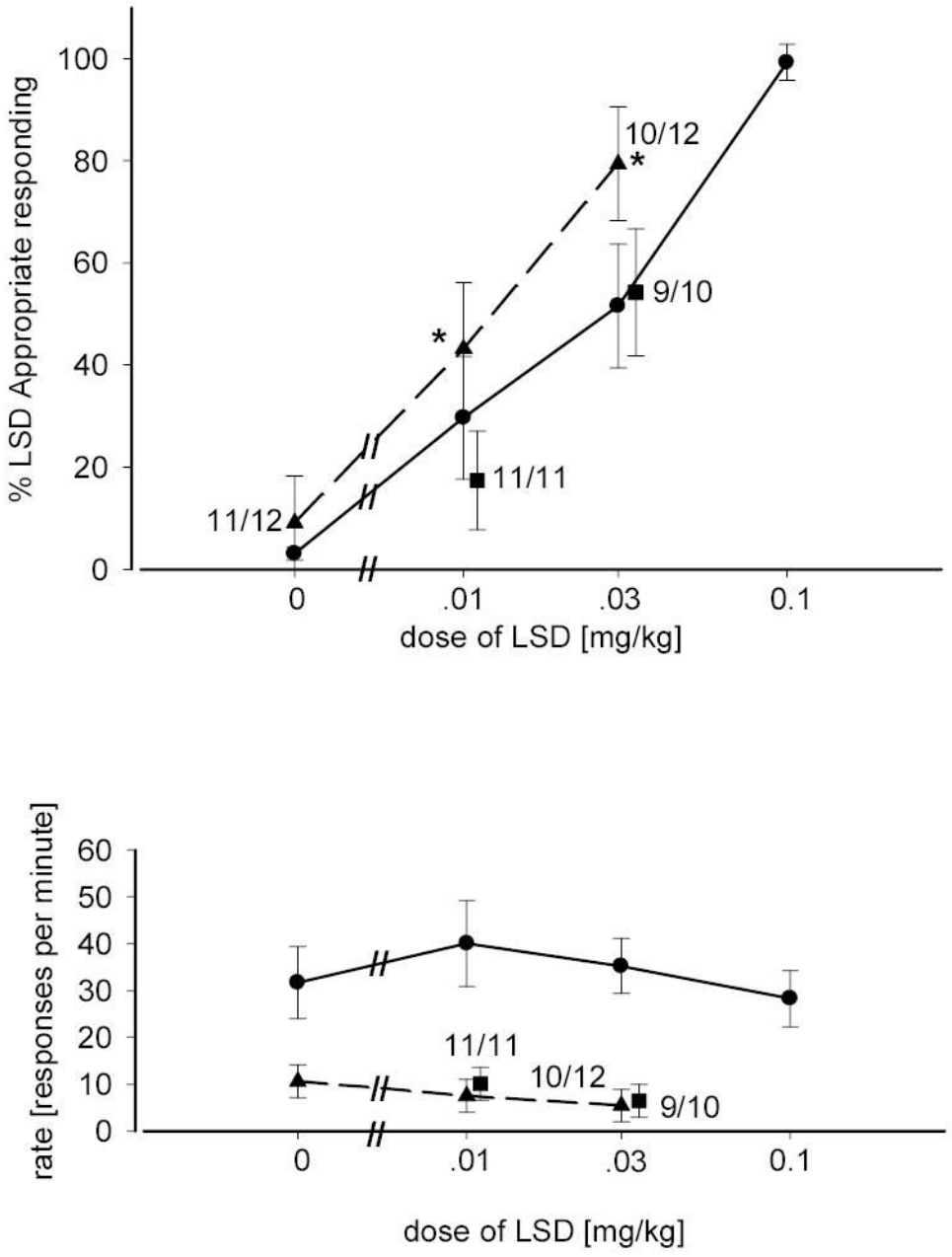

Fig 4.

Dose-response relationship for LSD alone and in combination with gepirone. *Circles* represent the effects of LSD alone in rats trained with LSD as a discriminative stimulus (0.1 mg/kg). *Triangles* represent the effects of LSD given in combination with gepirone (0.3 mg/kg). *Squares* represent the effects of LSD in combination with gepirone and WAY-100,635. Other details are as described in figure 2.

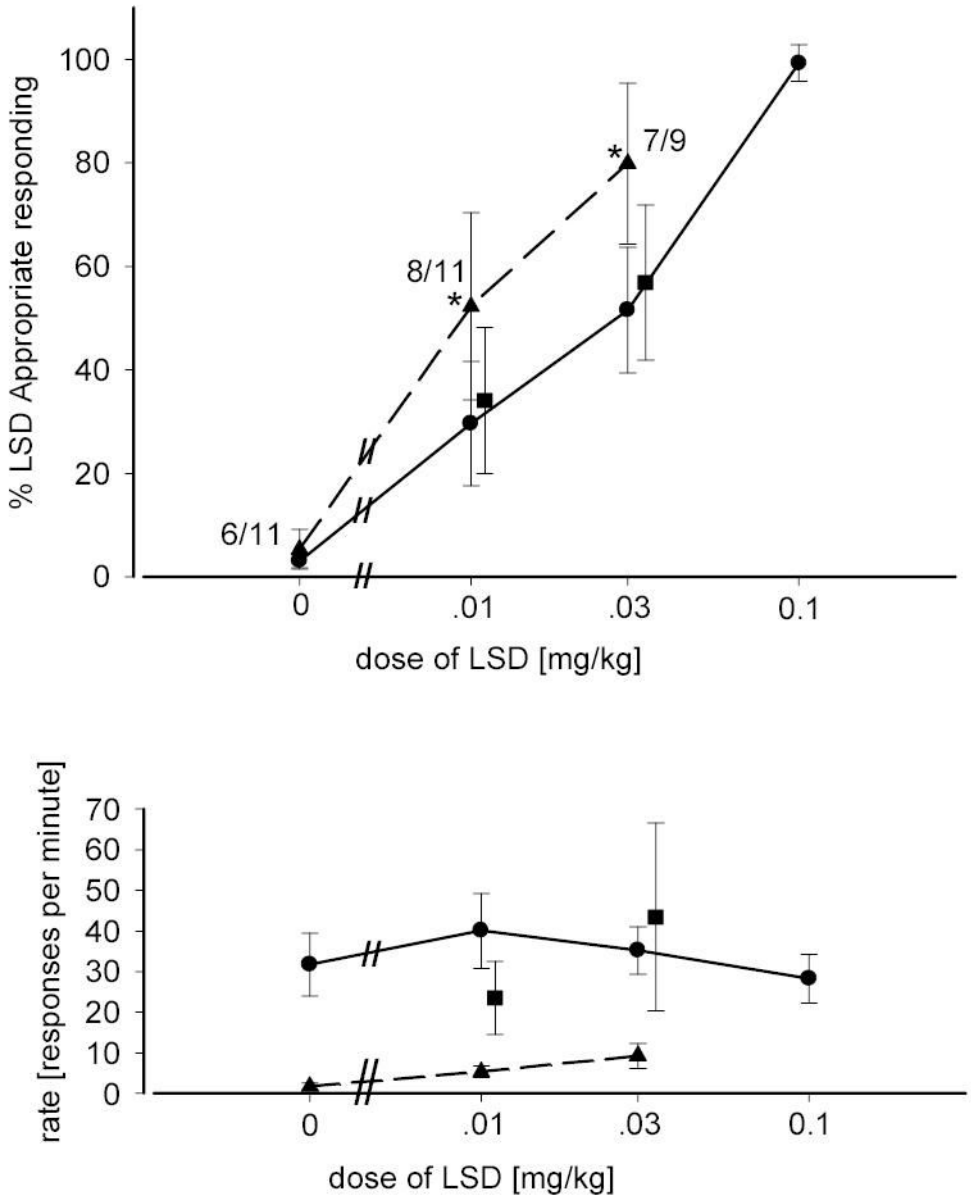

Fig 5.

Dose-response relationship for LSD alone and in combination with ipsapirone. *Circles* represent the effects of LSD alone in rats trained with LSD as a discriminative stimulus (0.1mg/kg). *Triangles* represent the effects of LSD given in combination with ipsapirone (0.3 mg/kg). *Squares* represent the effects of LSD in combination with ipsapirone and WAY-100,635. Other details are as described in figure 2.